Clinical Analysis of Adverse Drug Reactions

Karim Anton Calis, Pharm.D., M.P.H.
National Institutes of Health

March 12, 2009

Objectives

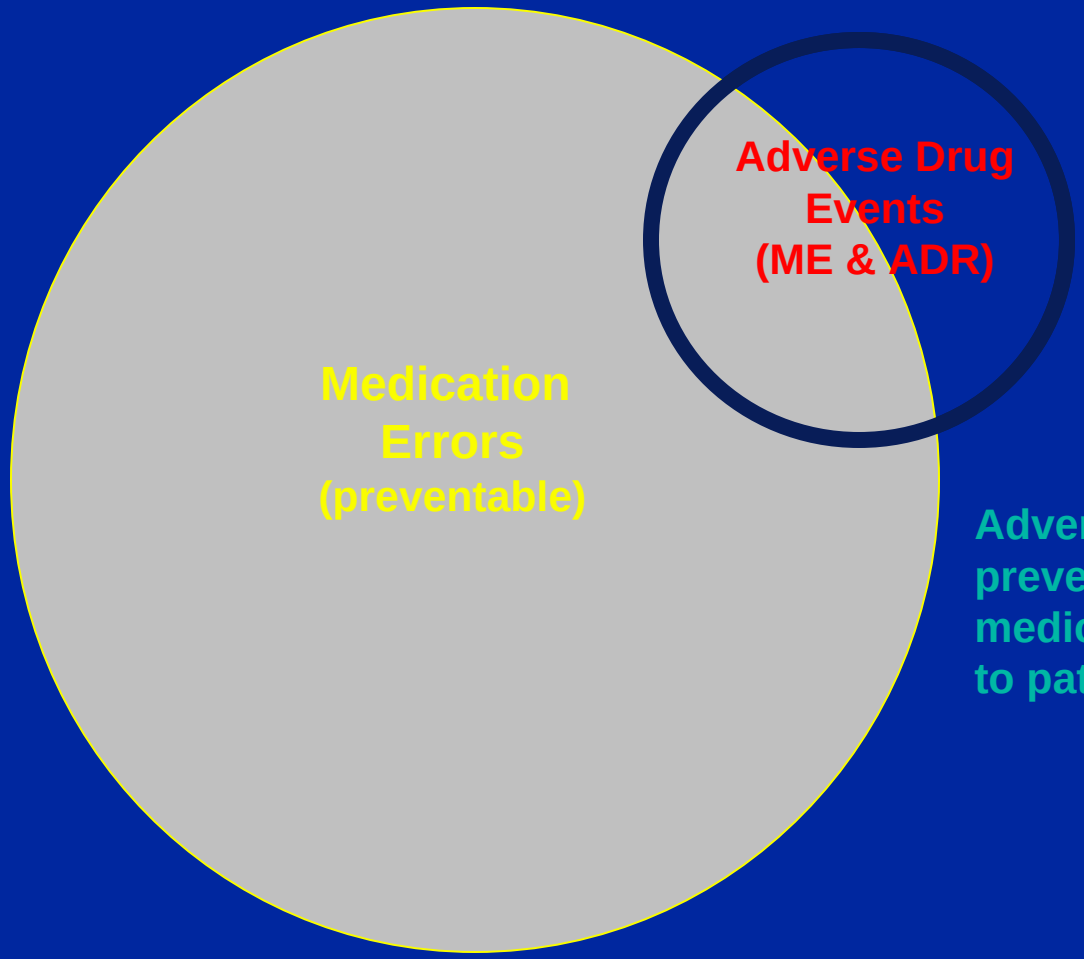
- Define adverse drug reactions
- Discuss epidemiology and classification of ADRs
- Describe basic methods to detect, evaluate, and document ADRs

Definition

- **WHO**
  - **response to a drug that is *noxious and unintended* and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function**
  - **excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors**

Adverse Drug Events

Adapted from Bates et al.



Adverse Drug Event: preventable or unpredicted medication event---with harm to patient

Epidemiology of ADRs

- substantial morbidity and mortality
- estimates of incidence vary with study methods, population, and ADR definition
- 4th to 6th leading cause of death among hospitalized patients*
- 6.7% incidence of serious ADRs*
- 0.3% to 7% of all hospital admissions
- annual dollar costs in the billions
- 30% to 60% are preventable

*JAMA. 1998;279:1200-1205.

Classification

- Onset
- Severity
- Type

Classification

- **Onset of event:**
  - **Acute**
    - **within 60 minutes**
  - **Sub-acute**
    - **1 to 24 hours**
  - **Latent**
    - **> 2 days**

Classification - Severity

- Severity of reaction:
  - Mild
    - » bothersome but requires no change in therapy
  - Moderate
    - » requires change in therapy, additional treatment, hospitalization
  - Severe
    - » disabling or life-threatening

Classification - Severity

- FDA Serious ADR
  - Result in death
  - Life-threatening
  - Require hospitalization
  - Prolong hospitalization
  - Cause disability
  - Cause congenital anomalies
  - Require intervention to prevent permanent injury

Classification

- Type A
  - » extension of pharmacologic effect
  - » often predictable and dose dependent
  - » responsible for at least two-thirds of ADRs
  - » e.g., propranolol and heart block, anticholinergics and dry mouth

Classification

- **Type B**
  - » **idiosyncratic or immunologic reactions**
  - » **rare and unpredictable**
  - » **e.g., chloramphenicol and aplastic anemia**

Classification

- Type C
  - » associated with long-term use
  - » involves dose accumulation
  - » e.g., phenacetin and interstitial nephritis or antimalarials and ocular toxicity

Classification

- Type D
  - » delayed effects (dose independent)
  - » Carcinogenicity (e.g., immunosuppressants)
  - » Teratogenicity (e.g., fetal hydantoin syndrome)

Classification

- Types of allergic reactions
  - Type I - immediate, anaphylactic (IgE)
    - » e.g., anaphylaxis with penicillins
  - Type II - cytotoxic antibody (IgG, IgM)
    - » e.g., methyldopa and hemolytic anemia
  - Type III - serum sickness (IgG, IgM)
    - » antigen-antibody complex
    - » e.g., procainamide-induced lupus
  - Type IV - delayed hypersensitivity (T cell)
    - » e.g., contact dermatitis

Classification - Type

Reportable

- All significant or unusual adverse drug reactions as well as unanticipated or novel events that are suspected to be drug related

Classification - Type

Reportable

- Hypersensitivity
- Life-threatening
- Cause disability
- Idiosyncratic
- Secondary to Drug interactions
- Unexpected detrimental effect
- Drug intolerance
- Any ADR with investigational drug

Common Causes of ADRs

- Antibiotics
- Antineoplastics*
- Anticoagulants
- Cardiovascular drugs*
- Hypoglycemics
- Antihypertensives
- NSAID/Analgesics
- Diagnostic agents
- CNS drugs*

*account for 69% of fatal ADRs

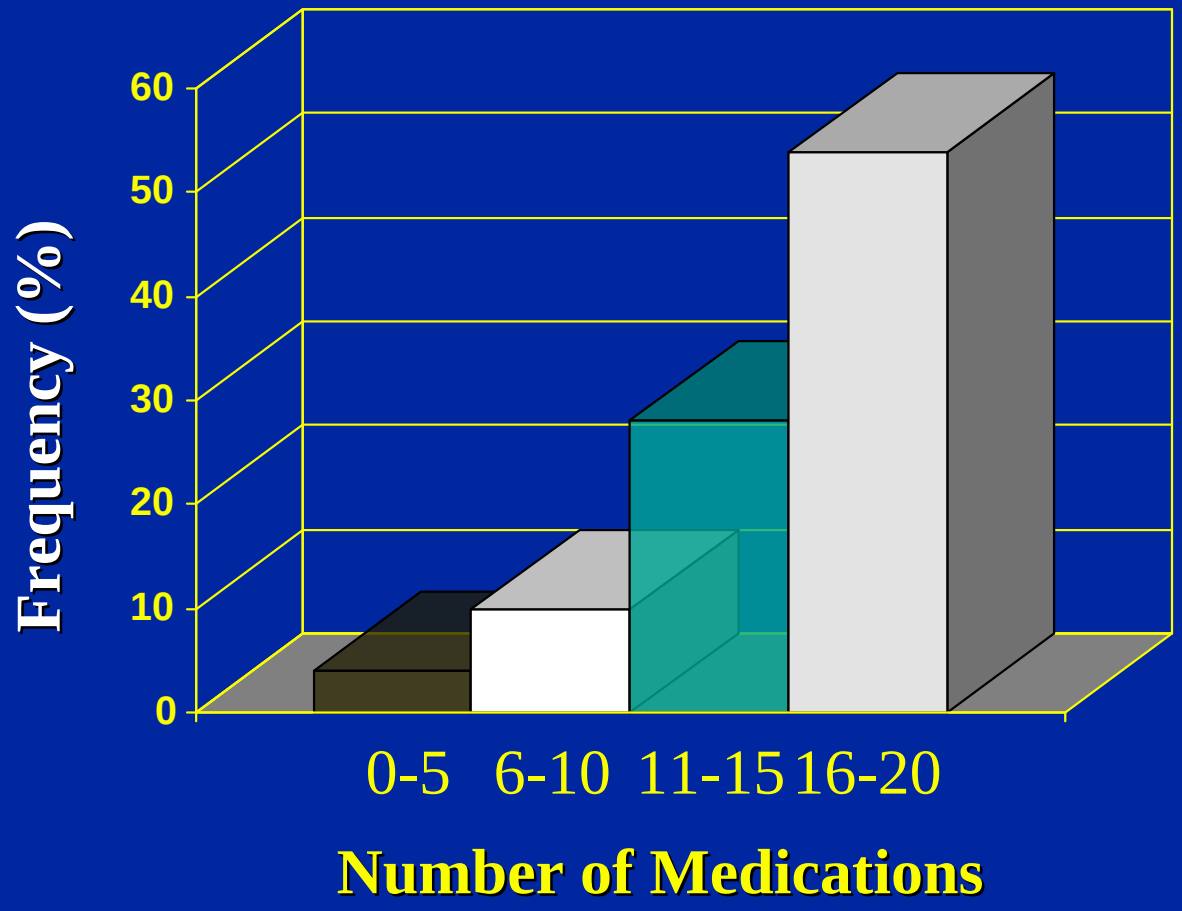
Body Systems Commonly Involved

- Hematologic
- CNS
- Dermatologic/Allergic
- Metabolic
- Cardiovascular
- Gastrointestinal
- Renal/Genitourinary
- Respiratory
- Sensory

ADR Risk Factors

- Age (children and elderly)
- Multiple medications
- Multiple co-morbid conditions
- Inappropriate medication prescribing, use, or monitoring
- End-organ dysfunction
- Altered physiology
- Prior history of ADRs
- Extent (dose) and duration of exposure
- Genetic predisposition

ADR Frequency by Drug Use



May FE. Clin Pharmacol Ther 1977;22:322-8

ADR Detection

- Subjective report
  - patient complaint
- Objective report:
  - direct observation of event
  - abnormal findings
    - » physical exam
    - » laboratory test
    - » diagnostic procedure

ADR Detection

- Medication order screening
  - abrupt medication discontinuation
  - abrupt dosage reduction
  - orders for “tracer” or “trigger” substances
  - orders for special tests or serum drug concentrations
- Spontaneous reporting
- Medication utilization review
  - Computerized screening
  - Chart review and concurrent audits

ADR Detection in Clinical Trials

- **Methods**
  - **Standard laboratory tests**
  - **Diagnostic tests**
  - **Complete history and physical**
  - **Adverse drug event questionnaire**
    - » **Extensive checklist of symptoms categorized by body system**
    - » **Review-of-systems approach**
    - » **Qualitative and quantitative**

ADR Detection in Clinical Trials

Limitations

- exposure limited to few individuals
  - » rare and unusual ADRs not detected
  - » 3000 patients at risk are needed to detect ADR with incidence of 1/1000 with 95% certainty
- exposure is often short-term
  - » latent ADRs missed
- external validity
  - » may exclude children, elderly, women of child-bearing age; and patients with severe form of disease, multiple co-morbidities, and those taking multiple medications

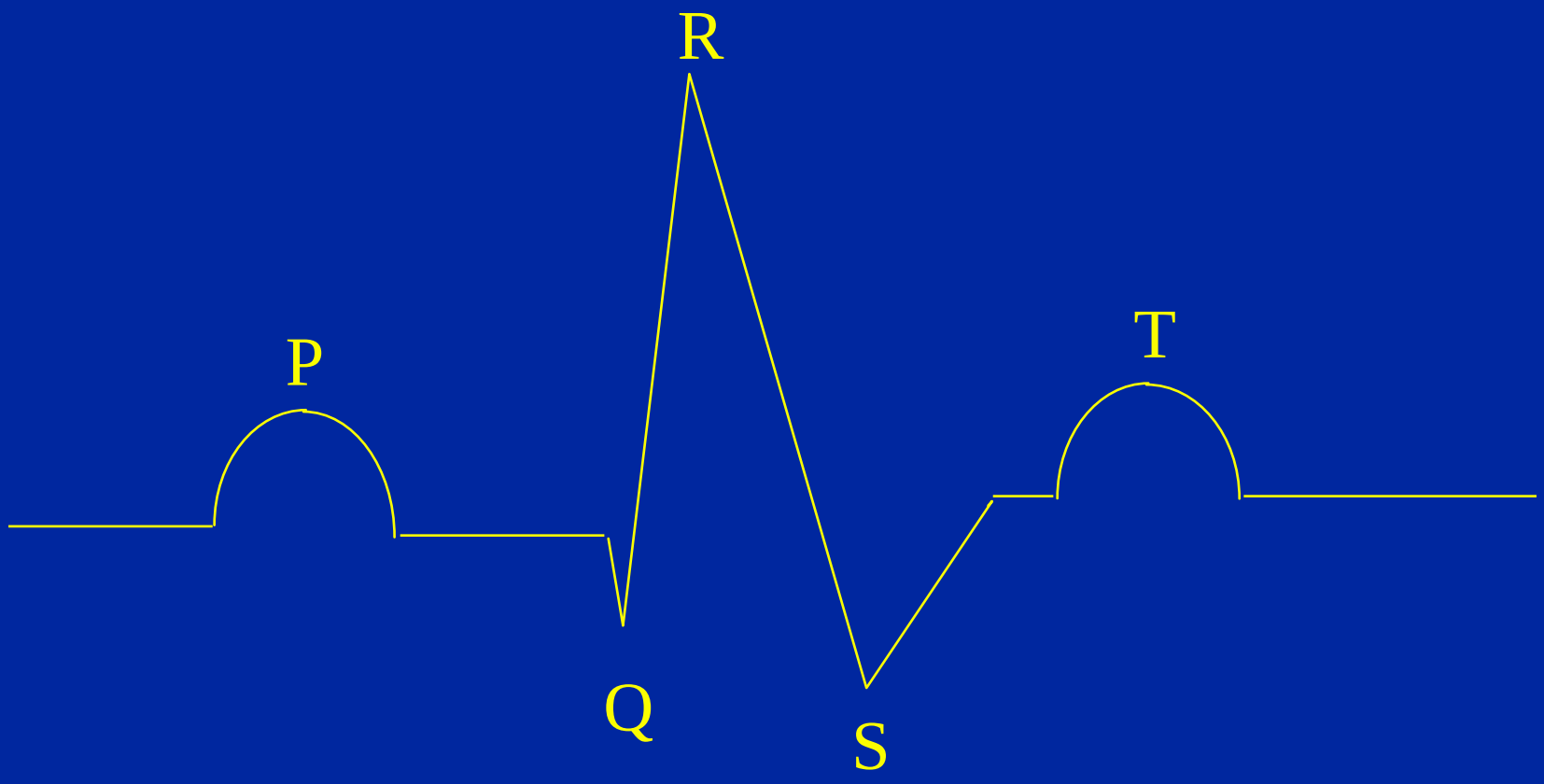
Preliminary Assessment

- **Preliminary description of event:**
  - **Who, what, when, where, how?**
  - ***Who* is involved?**
  - ***What* is the most likely causative agent?**
    - **Is this an exacerbation of a pre-existing condition?**
    - **Alternative explanations / differential diagnosis**
  - ***When* did the event take place?**
  - ***Where* did the event occur?**
  - ***How* has the event been managed thus far?**

Preliminary Assessment

- **Determination of urgency:**
  - **What is the patient's current clinical status?**
  - **How severe is the reaction?**
- **Appropriate triage:**
  - **Acute (ER, ICU, Poison Control)**

Detailed Description of Event PQRSTA Acronym



Detailed Description of Event

- History of present illness
- Signs / Symptoms: PQRSTA
  - Provoking or palliative factors
  - Quality (character or intensity)
  - Response to treatment, Radiation, Reports in literature
  - Severity / extent, Site (location)
  - Temporal relationship (onset, duration, frequency)
  - Associated signs and symptoms

Pertinent Patient/Disease Factors

- **Demographics**
  - age, race, ethnicity, gender, height, weight
- **Medical history and physical exam**
  - Concurrent conditions or special circumstances
    - » e.g., dehydration, autoimmune condition, HIV infection, pregnancy, dialysis, breast feeding
  - Recent procedures or surgeries and any resultant complications
    - » e.g., contrast material, radiation treatment, hypotension, shock, renal insufficiency

Pertinent Patient/Disease Factors

- End-organ function
- Review of systems
- Laboratory tests and diagnostics
- Social history
  - » tobacco, alcohol, substance abuse, physical activity, environmental or occupational hazards or exposures
- Pertinent family history
- Nutritional status
  - » special diets, malnutrition, weight loss

Pertinent Medication Factors

- Medication history
  - Prescription medications
  - Non-prescription medications
  - Alternative and investigational therapies
  - Medication use within previous 6 months
  - Allergies or intolerances
  - History of medication reactions
  - Adherence to prescribed regimens
  - Cumulative mediation dosages

Pertinent Medication Factors

- Medication
  - Indication, dose, diluent, volume
- Administration
  - Route, method, site, schedule, rate, duration
- Formulation
  - Pharmaceutical excipients
    - e.g., colorings, flavorings, preservatives
  - Other components
    - e.g., DEHP, latex

Pertinent Medication Factors

- Pharmacology
- Pharmacokinetics (LADME)
- Pharmacodynamics
- Adverse effect profiles
- Interactions
  - drug-drug
  - drug-nutrient
  - drug-lab test interference
- Cross-allergenicity or cross-reactivity

ADR Information

- Incidence and prevalence
- Mechanism and pathogenesis
- Clinical presentation and diagnosis
- Time course
- Dose relationship
- Reversibility
- Cross-reactivity/Cross-allergenicity
- Treatment and prognosis

ADR Information Resources

- **Tertiary**
  - » **Reference books**
    - – **Medical and pharmacotherapy textbooks**
    - – **Package inserts, PDR, AHFS, USPDI**
    - – **Specialized ADR resources**
      - **Meyler's Side Effects of Drugs**
      - **Textbook of Adverse Drug Reactions**
    - – **Drug interactions resources**
    - – **Micromedex databases (e.g., TOMES, POISINDEX, DRUGDEX)**
  - » **Review articles**

ADR Information Resources

- **Secondary**
  - **MEDLARS databases (e.g., Medline, Toxline, Cancerline, Toxnet)**
  - **Excerpta Medica's Embase**
  - **International Pharmaceutical Abstracts**
  - **Current Contents**
  - **Biological Abstracts (Biosis)**
  - **Science Citation Index**
  - **Clin-Alert and Reactions**

ADR Information Resources

- **Primary**
  - » **Spontaneous reports or unpublished data**
    - – **FDA**
    - – **Manufacturer**
  - » **Anecdotal and descriptive reports**
    - – **Case reports, case series**
  - » **Observational studies**
    - – **Case-control, cross-sectional, cohort**
  - » **Experimental and other studies**
    - – **Clinical trials**
    - – **Meta-analyses**

Causality Assessment

- Prior reports of reaction
- Temporal relationship
- De-challenge
- Re-challenge
- Dose-response relationship
- Alternative etiologies
- Objective confirmation
- Past history of reaction to same or similar medication

Causality Assessment

- Examples of causality algorithms
  - Kramer
  - Naranjo and Jones
- Causality outcomes
  - Highly probable
  - Probable
  - Possible
  - Doubtful

Naranjo ADR Probability Scale

Naranjo CA. Clin Pharmacol Ther 1981;30:239-45

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

		Yes	No	Do Not Know	Score
1.	Are there previous *conclusive* reports on this reaction?	+1	0	0	____
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	____
3.	Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	____
4.	Did the adverse reactions appear when the drug was readministered?	+2	-1	0	____
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	____
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	____
7.	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	____
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	____
9.	Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	____
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	____
				Total Score	____

Total Score	*ADR Probability Classification*
9	Highly Probable
5-8	Probable
1-4	Possible
0	Doubtful

Management Options

- Discontinue the offending agent if:
  - it can be safely stopped
  - the event is life-threatening or intolerable
  - there is a reasonable alternative
  - continuing the medication will further exacerbate the patient's condition
- Continue the medication (modified as needed) if:
  - it is medically necessary
  - there is no reasonable alternative
  - the problem is mild and will resolve with time

Management Options

- Discontinue non-essential medications
- Administer appropriate treatment
  - » e.g., atropine, benztropine, dextrose, antihistamines, epinephrine, naloxone, phenytoin, phytonadione, protamine, sodium polystyrene sulfonate, digibind, flumazenil, corticosteroids, glucagon
- Provide supportive or palliative care
  - » e.g., hydration, glucocorticoids, warm / cold compresses, analgesics or antipruritics
- Consider rechallenge or desensitization

Follow-up and Re-evaluation

- Patient’s progress
- Course of event
- Delayed reactions
- Response to treatment
- Specific monitoring parameters

Documentation and Reporting

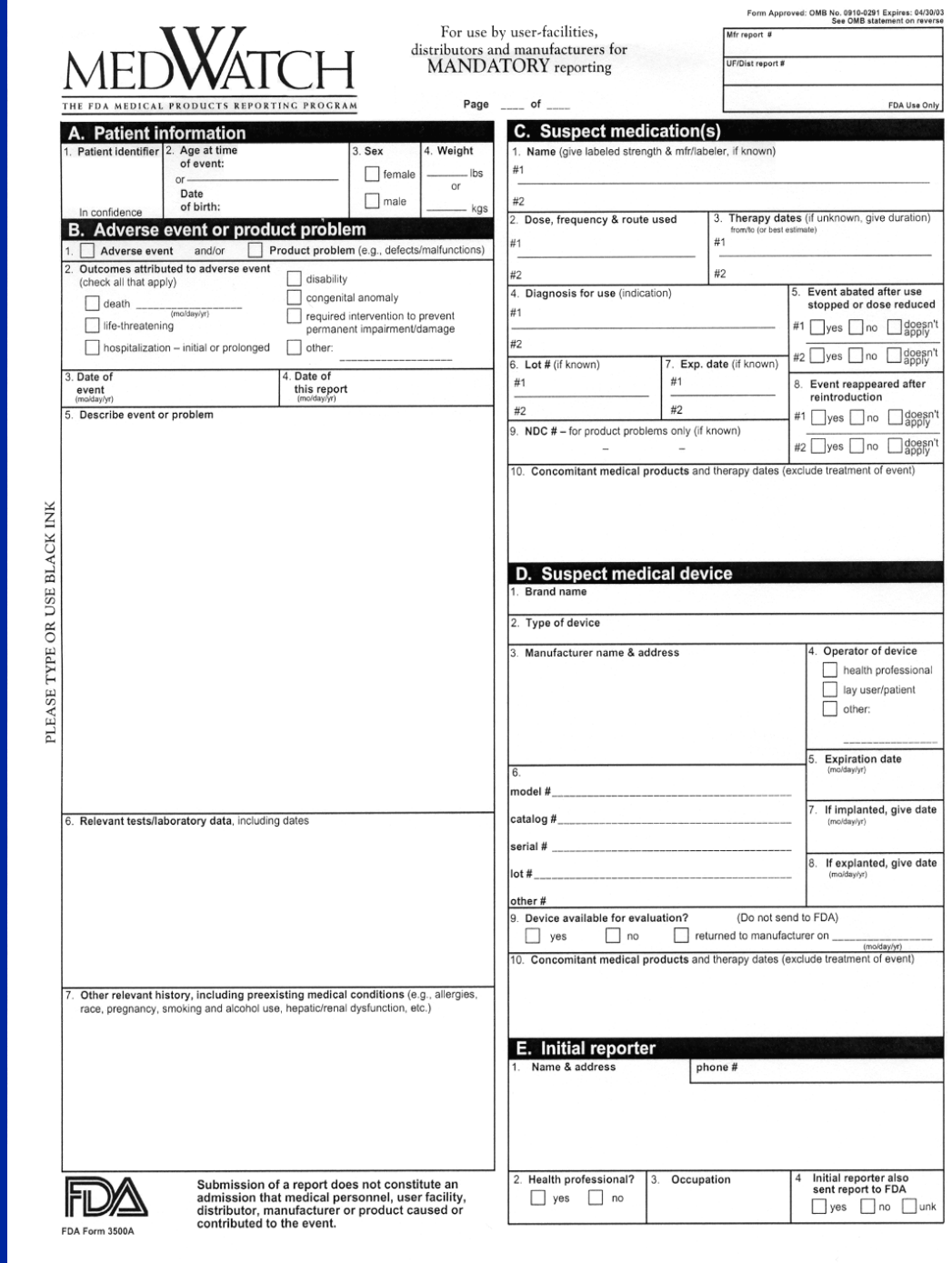
- Medical record
  - Description
  - Management
  - Outcome
- Reporting responsibility
  - JCAHO-mandated reporting programs
  - Food and Drug Administration
    - » post-marketing surveillance
    - » particular interest in serious reactions involving new chemical entities
  - Pharmaceutical manufacturers
  - Publishing in the medical literature

Components of an ADR Report

- Product name and manufacturer
- Patient demographics
- Description of adverse event and outcome
- Date of onset
- Drug start and stop dates/times
- Dose, frequency, and method
- Relevant lab test results or other objective evidence
- De-challenge and re-challenge information
- Confounding variables

MEDWATCH 3500A Reporting Form

https://www.accessdata.fda.gov/scripts/medwatch



Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Mfr report #
UF/Dist report #
FDA Use Only

Page ____ of ____

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: / or Date of birth:
3. Sex — female / male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - death ____ (mo/day/yr)
   - life-threatening
   - hospitalization – initial or prolonged
   - disability
   - congenital anomaly
   - required intervention to prevent permanent impairment/damage
   - other: ____
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) #1 / #2
2. Dose, frequency & route used #1 / #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate) #1 / #2
4. Diagnosis for use (indication) #1 / #2
5. Event abated after use stopped or dose reduced #1 yes no doesn't apply / #2 yes no doesn't apply
6. Lot # (if known) #1 / #2
7. Exp. date (if known) #1 / #2
8. Event reappeared after reintroduction #1 yes no doesn't apply / #2 yes no doesn't apply
9. NDC # – for product problems only (if known) – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device — health professional / lay user/patient / other: ____
5. Expiration date (mo/day/yr)
6. model # ____ catalog # ____ serial # ____ lot # ____ other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA) yes no returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

1. Name & address — phone #
2. Health professional? yes no
3. Occupation
4. Initial reporter also sent report to FDA yes no unk

FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.